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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Acetic Acid Derivatives

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(57) 15 Claims

page 5 q: claimed compound

Notice: The specification contained herein as filed

Canada

Abstract

Acetic acid derivatives of the formula

$$H_2N(NH)C\text{-}X\text{-}Y\text{-}CO\text{-}Z\text{-}CH(Q^1)COOQ^2 \qquad I$$

in which X, Y, Z, Q^1 and Q^2 have the meaning indicated in the description, and hydrates, solvates and physiologically utilisable salts thereof inhibit the binding of adhesive proteins to blood platelets and also inhibit blood platelet aggregation and cell-cell adhesion. They are prepared by removal of protecting groups in appropriate compounds containing ester groups and protected amidino groups.

The present invention relates to new acetic acid derivatives, to processes for their preparation, to pharmaceutical preparations which contain such compounds, and to the use of these compounds for the production of pharmaceutical preparations.

The invention relates in particular to acetic acid derivatives of the formula

$H_2N(NH)C\text{-}X\text{-}Y\text{-}CO\text{-}Z\text{-}CH(Q^1)COOQ^2$ (I)

in which

Q^1 is hydrogen, methyl or phenyl,

Q^2 is hydrogen, phenyl-lower alkyl or lower alkyl which can be cleaved under physiological conditions,

X is 1,4-phenylene, 1,4-piperidinylene bound via the C atom in the 4-position to the group Y, or 2,5- or 3,6-pyridylene

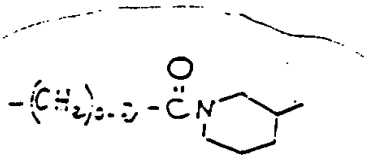
Y is a group of the formula

$-(CH_2)_{0\text{-}2}\text{-}CONHCH(Q^3)(CH_2)_{1\text{-}3}\text{-}$ (Y^1)

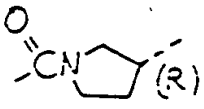
$-CONHCH_2CH(Q^4)\text{-}$ (Y^2)

$-(CH_2)_2NHCOCH_2\text{-}$ (Y^3)

$-NHCO(CH_2)_3\text{-}$ (Y^4)

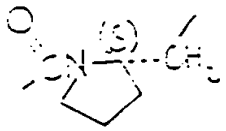


(Y^5)



(Y^6)

or



(Y^7)

Q^3 is hydrogen, methyl, phenyl, -COOH, -COO-lower alkyl, -CONH$(CH_2)_2$-COOH or -CONH$(CH_2)_2$-COO-lower alkyl,

Q^4 is hydrogen, methyl or phenyl,

Z is a 1,4-piperazinylene group, a 1,4-piperidinylene group bound via the N-atom in the 1-position to the CO group, or a group of the formula -NHCH(R^1)- or -NHCH(COR^2)-

R^1 is hydrogen, methyl, phenyl or -COO-lower alkyl,

R^2 is the radical of an α-aminocarboxylic acid bound via the amino group or an ester or amide thereof, or a group of the formula -NHCH_2CH_2-Ar, or -CO-R^2 is an optionally mono- or di-lower-alkylated carbamoyl group or a pyrrolidinoyl or piperidinoyl group,

Ar is phenyl or phenyl which is substituted by lower alkyl, lower alkoxy, -COOH, -COO-lower alkyl, -O$(CH_2)_{1-4}$-COOH, -O$(CH_2)_{1-4}$-COO-lower alkyl, -$CONH_2$, -CONH-lower alkyl, -CON(lower alkyl)$_2$, pyrrolidinoyl or piperidinoyl,

and hydrates or solvates and physiologically utilisable salts thereof.

In the context of the present invention, tBu denotes t-butyl, Boc denotes t-butoxycarbonyl, Z denotes benzyloxycarbonyl, Val denotes L-valyl, Phe denotes L-phenylalanyl, Ser denotes L-seryl, Gly denotes glycyl, Ala denotes L-alanyl, Asp denotes L-α-aspartyl, Leu denotes L-leucine and Tyr denotes L-tyrosine.

The expression "lower" denotes groups having 1-6, preferably 1-4, C atoms. Examples of lower alkyl groups are methyl, ethyl, propyl, isopropyl and n-, s- or t-butyl. Examples of lower alkyl groups which can be cleaved under physiological conditions are primary and secondary lower alkyl groups.

Examples of α-aminocarboxylic acid radicals bound via the amino

group are Val, Phe, Ser, Leu, Tyr and their corresponding lower alkyl or phenyl-lower alkyl esters, amides and mono- or di-lower alkyl amides.

The compounds of the formula I can be solvated, in particular hydrated. Hydration can take place in the course of the preparation process or occur gradually as a consequence of hygroscopic properties of an initially anhydrous compound of the formula I.

Examples of physiologically utilisable salts of the compounds of the formula I are salts with physiologically tolerable mineral acids, such as hydrochloric acid, sulphuric acid or phosphoric acid, or with organic acids, such as methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, succinic acid or salicylic acid. The compounds of the formula I can also form salts with physiologically tolerable bases. Examples of such salts are alkali metal, alkaline earth metal, ammonium and alkylammonium salts, such as the Na, K, Ca or tetramethylammonium salt. The compounds of the formula I contain an amidino group and can therefore be present in the form of zwitterions.

The compounds of the formula I, which contain one or more asymmetric C atoms, can be present as enantiomers, as diastereomers or as mixtures thereof, for example as racemates.

Preferred compounds of the formula I are those of the formula

$H_2N(HN)C$-X-Y^a-CONHCH(R^{11})CH_2COOR^{21} I-A

in which

X is 1,4-phenylene or 1,4-piperidinylene bound via the C atom in the 4-position to the group Y^a,

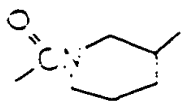
Y^a is a group of the formula

-$(CH_2)_{0-1}$-CONHCH(Q^a)$(CH_2)_{1-2}$- (Y^{11})

-$(CH_2)_2$NHCOCH_2- (Y^3)

-NHCO$(CH_2)_3$- (Y^4)

or



(Y51)

Q^a is hydrogen or phenyl,

R^{11} is hydrogen or -CO-R^{22},

R^{22} is the radical of an α-aminocarboxylic acid bound via the amino group or of an ester or amide thereof, and

Q^{21} is hydrogen or lower alkyl which can be cleaved under physiological conditions.

In the formula I, Y is preferably a group of the formula Y^1, in particular -CONH$(CH_2)_{2-4}$-, -CH_2CONH$(CH_2)_2$-, -CONHCH$(C_6H_5)CH_2$-, -CONHCH(CONHCH$_2$CH$_2$COOH)CH$_2$-, -CONHCH(COOH)CH$_2$- or -CONHCH$(CH_3)CH_2$-.

In the formula I, Z is preferably a group of the formula -NHCH$_2$-, -NHCH(CH_3)-, -NHCH(C_6H_5)-, -NHCH(COO-isobutyl)-, -NHCH(CO-Val)-, -NHCH(CO-Phe)-, -NHCH(CO-Tyr)-, -NHCH(CO-Ser-OC_2H_5)-, -NHCH(CO-Leu-O-isopropyl)-, -NHCH(CONHCH$_2$CH$_2$-C_6H_4-OCH_3)-, -NHCH(CONHCH$_2$CH$_2$-C_6H_4-COOH)-, -NHCH(CONHCH$_2$CH$_2$-C_6H_4-OCH_2COOH)-, -NHCH($CONH_2$)- or -NHCH(pyrrolidinoyl)-.

Particularly preferred compounds of the formula I are the following:

N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine,

N-[N-[4-(p-amidinobenzamido)butyryl]-L-α-aspartyl]-L-valine,

N-[N-(p-amidinobenzoyl)-ß-alanyl]-ß-alanine,

N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-L-leucine isopropyl ester,

N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-L-valine,

N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-3-(p-hydroxyphenyl)-L-alanine,

N-[N-[5-(p-amidinobenzamido)valeryl]-L-α-aspartyl]-3-phenyl-L-

alanine,
i obutyl N-[5-(p-amidinobenzamido)valeryl]-L-α-aspartate,
N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-L-serine ethyl ester
and
N-[N-[[(R)-1-(p-amidinobenzoyl)-3-pyrrolidinyl]-carbonyl]-L-α-aspartyl]-3-phenyl-L-alanine.

Further examples of compounds of the formula I are the following:
N-[N-[N-(1-amidino-4-piperidinylcarbonyl)-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine,
N-[N-[N-(p-amidinophenylacetyl)-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine,
N-[N-[4-(p-amidinophenylcarbamoyl)butyryl]-L-α-aspartyl]-3-phenyl-L-alanine,
N-[N-[(p-amidinophenylcarbamoyl)acetyl]-L-α-aspartyl]-3-phenyl-L-alanine,
rac-N-[1-(p-amidinobenzoyl)-3-piperidinyl-carbonyl]-ß-alanine,
N-[4-(p-amidinobenzamido)butyryl]-ß-alanine,
N-[(DL)-N-(p-amidinobenzoyl)-3-phenyl-ß-alanyl]-ß-alanine,
N,N'-[(S)-(p-amidinobenzamido)ethylene]dicarbonyl]di-ß-alanine,
2-N-(p-amidinobenzoyl)-4-N-(2-carboxyethyl)-L-asparagine,
N-[5-(p-amidinobenzamido)valeryl]-ß-alanine,
rac-N-[[1-[3-(1-amidino-4-piperidinyl)propionyl]-3-piperidinyl]carbonyl]-ß-alanine,
N-[[(S)-1-(p-amidinobenzoyl)-2-pyrrolidinyl]-acetyl]-ß-alanine,
(S)-3-[[N-(p-amidinobenzoyl)-ß-alanyl]amino-3-[(p-methoxyphenethyl)carbamoyl]propionic acid,
N-[[(R)-1-(p-amidinobenzoyl)-3-pyrrolidinyl]-carbonyl]-ß-alanine,
N-[N-(p-amidinobenzoyl)-2-methyl-ß-alanyl]-L-α-aspartamide,
N-[N-[(p-amidinophenyl)acetyl]-ß-alanyl]-ß-alanine.

rac-N-[[[1-(p-amidinophenyl)acetyl]-3-piperid...yl]-carbonyl]-ß-alanine benzyl ester,

rac-N-[[1-[(p-amidinophenyl)acetyl]-3-piperidinyl]-carbonyl]-ß-alanine,

N-[N-[N-[3-(1-amidino-4-piperidinyl)propionyl]-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine,

(S)-ß-[[DL-N-(p-amidinobenzoyl)-3-methyl-ß-alanyl]amino]-γ-oxo-1-pyrrolidinebutyric acid,

DL-N-[N-(p-amidinobenzoyl)-ß-alanyl]-3-methyl-ß-alanine,

N-[DL-N-(p-amidinobenzoyl)-2-phenyl-ß-alanyl]-ß-alanine,

DL-N-[N-(p-amidinobenzoyl)-ß-alanyl]-2-methyl-ß-alanine,

DL-N-[N-(p-amidinobenzoyl)-ß-alanyl]-2-phenyl-ß-alanine,

p-[2-[[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-amino]ethyl]benzoic acid,

DL-N-[N-(p-amidinobenzoyl)-ß-alanyl-3-phenyl-ß-alanine,

[p-[2-[[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]amino]ethyl]-phenoxy]acetic acid,

1-[N-(p-amidinobenzoyl)-ß-alanyl]-4-piperidineacetic acid,

4-[N-(p-amidinobenzoyl)-ß-alanyl]-1-piperazineacetic acid and

N-[N-[N-[(5-amidino-2-pyridyl)carbonyl]-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine.

The above compounds can be obtained according to the invention by cleaving at least one protecting group from a compound of the formula

$$X'\text{-}Y\text{-}CO\text{-}Z'\text{-}CH(Q^1)\text{-}COO\text{-}Q^5 \qquad II$$

in which

Q^1 and Y have the meaning indicated further above,

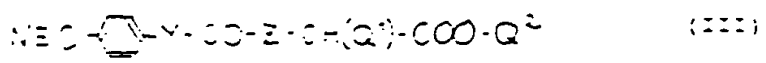
X' is phenyl or 4-piperidinyl which is substituted in the 4-position by an optionally protected amidino group, and

Z' and Q^5 have the same meaning as indicated further above for Z and Q^2,

or

b) converting the nitrile group into the amidino group in a nitrile of the

formula



and, if desired, converting a compound of the formula I into a physiologically tolerable salt or converting a salt of a compound of the formula I into the free acid or base.

Examples of protecting groups in the compounds of the formula II are the benzyl or lower alkyl groups, such as t-butyl, contained in the ester groups benzyl-OCO- or t-Bu-OCO-; and amidino protecting groups, such as Z and Boc. Examples of protected amidino groups are -C(NH)NH-Z, -C(NH)NH-Boc and -C(N-Boc)-NH-Boc.

Ester groups can be cleaved in a manner known per se, for example by hydrolysis using a base, such as an alkali metal hydroxide, for example sodium hydroxide, in a solvent, such as methanol. Benzyl esters can be cleaved by hydrogenation in the presence of a noble metal catalyst, such as palladium on carbon (Pd/C) in a solvent, such as methanol, ethanol, formic acid or acetic acid, at a temperature up to about 40°C, preferably at room temperature. In this process, an amidino protecting group present in the group X', such as Z, is removed at the same time.

Ester groups, such as t-butyl, or amidino protecting groups, such as Boc, can be cleaved, for example, using an acid, such as formic acid or trifluoroacetic acid, if desired in a solvent, such as dichloromethane, at a temperature up to 40°C, preferably at room temperature.

The compounds of the formula II are new and likewise a subject of the present invention. They can be prepared starting from known compounds by methods which are known per se, for example as described below.

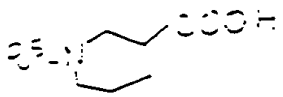
Thus, in a first step an amine of the formula

$$H\text{-}Z'\text{-}CH(Q^1)COO\text{-}Q^{22} \qquad IV$$

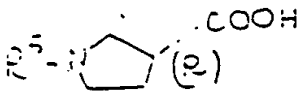
is coupled with an acid of the formula

$$R^5\text{-}NHCH(Q^{31})(CH_2)_{1\text{-}3}\text{-}COOH \qquad Va$$

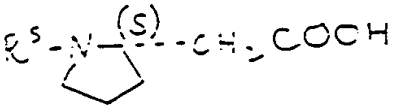
$$R^5\text{-}NHCH_2CH(Q^4)\text{-}COOH \qquad Vb$$



Vc

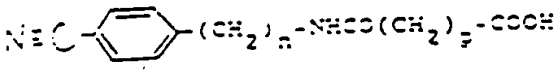


Vd



Ve

or



VI

in which

Q^{22} is an easily cleavable alkyl group,

Q^{31} is hydrogen, methyl, phenyl, -COO-lower alkyl, or $-CONH(CH_2)_2-COO$-lower alkyl,

R^3 is an amino protecting group, such as Z or Boc,

n = 0 and p = 3 or n = 2 and p = 1,

with the formation of an amide group by the methods known per se from peptide chemistry.

Thus, the coupling of IV with Va, Vb or VI can be carried out, for example, in tetrahydrofuran (THF) at -10°C to room temperature under argon in the presence of O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU). The coupling of IV with Vc, Vd or Ve is effected, for example, by initially activating the acid Vc, Vd or Ve in THF using chlorodimethoxytriazine and N-methylmorpholine and then reacting the product with the p-toluenesulphonate of the amine IV and N-methylmorpholine.

From the reaction product thus obtained, an amino protecting group R^3, for example Z or Boc, can then be selectively removed as described above by catalytic hydrogenation or by means of trifluoroacetic acid.

An amine of the formula

$$H_2NCH(Q^{31})(CH_2)_{n+1}-CO-Z'-CH(Q^1)COO-Q^{22} \qquad \text{VIII}$$

obtained in this manner, for example starting from IV and Va, can then be coupled with 4-cyanobenzoic acid or 4-cyanophenylacetic acid to give a nitrile, for example one of the formula III, for example as described above for the coupling of IV with Va.

A nitrile obtained in this way or a nitrile obtained by coupling IV and VI can be converted into a compound II in which X' contains a free amidino group, for example by reaction with hydrogen sulphide and triethylamine in pyridine to give the thioamide, methylation with methyl iodide in acetone and subsequent reaction with ammonium acetate in methanol. A nitrile III can be converted analogously into the corresponding compound of the formula I.

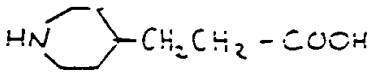
An amine of the above formula VIII can also be reacted, for example, with 1-amidino-4-piperidinecarboxylic acid, p-amidinophenacetyl chloride or p-amidinobenzoyl chloride to give a compound II in which X' is 1-amidino-4-piperidinyl or p-amidinophenyl.

An amine of the formula VIII or an amine of the formulae Va to Ve obtained starting from a compound of the formula IV and an acid can furthermore be reacted in methylene chloride/aqueous sodium bicarbonate solution with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate or with di-t-butyl dicarbonate in the presence of sodium carbonate to give a compound of the formula II in which X' is p-amidinophenyl protected by Z or Boc.

The compounds of the formulae IV-VI are known or can be prepared in analogy to the known compounds or as described in the examples below.

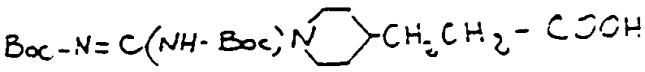
Thus, a nitrile VI can be prepared by coupling the appropriate amine of the formula $NCC_6H_4(CH_2)_n-NH_2$ with the appropriate acid of the formula $HOOC(CH_2)_p-COOQ^{22}$, for example analogously to the coupling of an amine IV with an acid V, followed by removal of the ester group Q^{22}.

To prepare a compound of the formula II in which X' is 4-piperidinyl substituted in the 4-position by a protected amidino group, a compound of the formula



IX

can first be reacted, for example, with N,N'-bis-(t-butoxycarbonyl)-S-methylisothiourea, in t-butanol and sodium hydroxide solution to give a compound of the formula

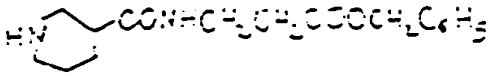


X

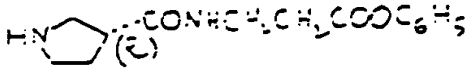
and the latter can then be coupled, for example, with a compound of the formula

$H_2NCH(Q^{2'})(CH_2)_{1-3}$-$CONHCH_2CH_2COOCH_2C_6H_5$ XIa

$H_2NCH_2CH(Q')CONHCH_2CH_2COOCH_2C_6H_5$ XIb



XIc



XId

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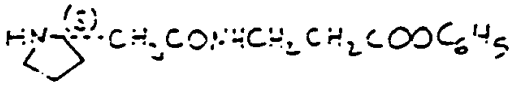


XIe

in which

$Q^{2'}$ is hydrogen, methyl, phenyl, -COO-lower alkyl or -$CONH(CH_2)_2$-COO-lower alkyl.

A compound of the formula II in which X' is a

phenyl or 4-piperidinyl which is substituted in the 4-position by a protected amidino group, can addi-tionally be prepared by coupling of an acid of the formula X'-Y-COOH with an amine of the above formula IV.

The compounds of the formula I, their solvates and their salts inhibit both the binding of fibrinogen, fibronectin and the Willebrand factor to the fibrinogen receptor of blood platelets (glycoprotein IIb/IIIa) and the binding thereof and of other adhesive proteins, such as vitronectine, collagen and laminine, to the corresponding receptors on the surface of different cell types. The said compounds thus influence cell-cell and cell-matrix interactions. They prevent in particular the formation of blood platelet thrombi and can be used in the control or prevention of diseases such as thrombosis, cerebral infarct, myocardial infarct, inflammation and arteriosclerosis. These compounds also have an effect on tumour cells in that they inhibit metastasis formation thereof. They can thus also be employed as anti-tumour agents. They can further accelerate the healing of wounds.

The inhibition of fibrinogen formation on the fibrinogen receptor, glycoprotein IIb/IIIa, can be detected as follows:

Glycoprotein IIb/IIIa is obtained from Triton X-100 extracts of human blood platelets and purified by lectin affinity chromatography (Analytical Biochemistry 151, 1985, 169-177) and chromatography on an Arg-Gly-Asp-Ser affinity column (Science 231, 1986, 1559-62). The receptor protein thus obtained is bound to microtiter plates. The specific binding of fibrinogen to the immobilised receptor is determined with the aid of an ELISA system ("enzyme-linked immunosorbent assay"). The IC_{50} values below correspond to the concentration of the test substance which is required in order to inhibit the binding of fibrinogen to the immobilised receptor by 50%:

Product from Example:	1	2	3	4	5	6	
IC_{50} (nM):	0.0003	0.13	0.045	0.038	0.01	0.01	0.027

Product from Example:	8	9	10	11	18	25	28	31	38	39
IC_{50} (nM)	0.10	0.005	0.022	0.0025	0.010	0.0067	0.005	0.0128	0.0036	0.0012

As mentioned at the beginning, the present invention likewise relates to medicaments containing a compound of the formula I, a solvate thereof or a salt thereof, and furthermore also to a process for the production of medicaments of this type, which is characterised in that one or more of the said compounds and, if desired, one or more other therapeutically useful substances are brought into a pharmaceutical administration form. The medicaments can be administered enterally, for example orally in the form of tablets, film tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions or suspensions, or rectally, for example in the form of suppositories, or as a spray. Adminstration, however, can also be carried out parenterally, for example in the form of injection solutions or as an infusion.

To prepare tablets, film tablets, coated tablets and hard gelatin capsules, the active compound can be mixed with pharmaceutically inert, inorganic or organic excipients. Lactose, cornflour or derivatives thereof, talc, stearic acid or its salts, for example, can be used as excipients of this type for tablets, coated tablets and hard gelatin capsules. Vegetable oils, waxes, fats, semi-solid and liquid polyols, for example, are suitable

as excipients for soft gelatin capsules; depending on the nature of the active compound, however, no excipients at all are necessary in the case of soft gelatin capsules. Water, polyols, sucrose, invert sugar and glucose, for example, are suitable as excipients for the production of solutions and syrups, water, alcohols, polyols, glycerol and vegetable oils, for example, are suitable for injection solutions, and natural or hardened oils, waxes, fats and semi-solid or liquid polyols, for example, are suitable for suppositories. The pharmaceutical preparations can in addition also contain preservatives, solubilisers, stabilisers, wetting agents, emulsifiers, sweeteners, colorants, flavourings, salts for changing the osmotic pressure, buffers, coatings or antioxidants.

For the control or prevention of the diseases mentioned further above, the dosage of the active compound can vary within wide limits and is naturally to be suited to the individual conditions in each individual case. In general, on oral administration a dose of about 0.1 to 20 mg/kg, preferably of about 0.5 to 4 mg/kg, per day may be suitable for adults, it also being possible, however, to exceed the upper limit just indicated if this should prove appropriate.

Example 1

15 ml of trifluoroacetic acid are added to a suspension of 100 mg of N-[N-[N-(p-amidinobenzoyl)-β-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide in 10 ml of dichloromethane. After 3 hours at room temperature, the solvents are evaporated and the residue is crystallised using ether. After recrystallisation from methanol/ethyl acetate, 32 mg of the trifluoroacetate of N-[N-[N-(p-amidinobenzoyl)-β-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine, m.p. 216-220°C (decomposition), are obtained.

The starting material can be prepared as follows:

a) 834 mg of HBTU and 0.24 ml of N-methylmorpholine are added at 0°C under argon to a solution of 446 mg of Z-β-Ala-OH and 785 mg of H-Asp(O-tBu)-Phe-O-tBu (obtained from the condensation of Z-Asp(O-tBu)-OH with H-Phe-O-tBu

followed by hydrogenolysis). After 5 hours, the mixture is concentrated and the residue is partitioned in ethyl acetate/5% $NaHCO_3$. The organic phase is washed with water and 1M $KHSO_4$. The organic extracts are dried, filtered and concentrated. The residue is recrystallised from ethyl acetate/diisopropyl ether, 592 mg of Z-β-Ala-Asp(O-tBu)-Phe-O-tBu, m.p. 138-139°C, being obtained.

b) By catalytic hydrogenation of the precursor (550 mg) in ethanol in the presence of 10% Pd/C, 417 mg of H-β-Ala-Asp(O-tBu)-Phe-O-tBu, MS: 464 $(M-H)^-$, are obtained after chromatography on silica gel using ethyl acetate/methanol 4:1-1:1.

c) By coupling 350 mg of the product from b) with 125 mg of 4-cyanobenzoic acid in the manner described in Example 1a), 293 mg of N-[3-(t-butoxycarbonyl)-N-[N-(p-cyanobenzoyl)-β-alanyl]-L-alanyl]-3-phenyl-L-alanine t-butyl ester, m.p. 74-76°C, are isolated after chromatography on silica gel using ethyl acetate.

d) A solution of 270 mg of the precursor in pyridine/triethylamine 15:1 is saturated with hydrogen sulphide. The solvents are removed after 24 hours and the residue is partitioned in ethyl acetate/5% $NaHCO_3$. The organic extracts are washed with water and with 1M potassium hydrogen sulphate solution, dried and concentrated. After chromatography of the residue on silica gel using ethyl acetate followed by recrystallisation from hexane, 230 mg of N-[3-(t-butoxycarbonyl)-N-[N-[p-thiocarbamoylbenzoyl]-β-alanyl]-L-alanyl]-3-phenyl-L-alanine t-butyl ester, m.p. 101-103°C, are obtained.

e) 2 ml of methyl iodide are added to a solution of 200 mg of the precursor in 15 ml of acetone. After 3 hours at boiling temperature, the mixture is allowed to cool to room temperature and the product is precipitated by addition of diethyl ether. 226 mg of N-[3-(t-butoxycarbonyl)-N-[N-[p-[1-(methylthio)formimidoyl]benzoyl]-β-alanyl]-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide, m.p. 139-140°C, are obtained.

f) 32 mg of ammonium acetate are added to a solution of 160 mg of the precursor in 10 ml of methanol. The

reaction mixture is kept at boiling temperature for 4 hours. After cooling to room temperature, the solution is filtered, concentrated and treated with diethyl ether. The precipitated product is filtered off and dried. 135 mg of hydroiodide of N-[N-[N-(p-amidinobenzoyl)-β-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanine t-butyl ester, m.p. 162-163°C, are obtained.

Example 2

By treatment with trifluoroacetic acid in methylene chloride as described in Example 1 and after crystallisation from methanol/diethyl ether, 26 mg of N-[N-[N-(1-amidino-4-piperidinylcarbonyl)-β-alanyl]-L-α-asparty1]-3-phenyl-L-alanine trifluoroacetate (2:3), m.p. 127-130°C, are obtained from 60 mg of N-[N-[N-(1-amidino-4-piperidinylcarbonyl)-β-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanine t-butyl ester.

The starting material is prepared as follows:

Coupling 86 mg of 1-amidino-4-piperidinecarboxylic acid (Belg. Pat. 893,282, Nippon Chemiphar Co. Ltd.) with 119 mg of H-β-Ala-Asp(O-tBu)-Phe-O-tBu (Example 1b) in dioxane in the presence of 58 mg of pyridinium hydrochloride in the manner described in Example 1a) yields 71 mg of N-[N-[N-(1-amidino-4-piperidinylcarbonyl)-β-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanyl t-butyl ester, MS: 617 $(M-H)^+$, after chromatography on silica gel using methylene chloride/methanol 1:1.

Example 3

By treatment with trifluoroacetic acid as described in Example 1, 36 mg of the trifluoroacetate of N-[N-[N-(p-amidinophenylacetyl)-β-alanyl]-L-α-asparty1]-3-phenyl-L-alanine, m.p. 218-220°C (from diethyl ether), are obtained from 50 mg of N-[N-[N-(p-amidinophenylacetyl)-β-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide.

The starting material can be prepared as follows:

a) By coupling 142 mg of 4-cyanophenylacetic acid with 371 mg of H-β-Ala-Asp(O-tBu)-Phe-O-tBu (Example 1b), 250 mg of N-[N-[N-(p-cyanophenylacetyl)-β-alanyl]-3-t-

butoxycarbonyl-L-alanyl]-3-phenyl-L-alanine t-butyl ester, m.p. 93-94°C, are obtained in the manner described in Example 1a) after chromatography on silica gel using ethyl acetate/methanol.

b) Thionation of 230 mg of the precursor as described in Example 1d) yields 160 mg of N-[N-[N-(p-thiocarbamoylphenylacetyl)-β-alanyl]-3-t-butoxycarbonyl-L-alanyl]-3-phenyl-L-alanine t-butyl ester, MS: 607 $(M+H)^+$, after chromatography on silica gel using ethyl acetate.

c) Methylation of 120 mg of the precursor analogously to Example 1e) gives 100 mg of N-[N-[N-(p-methylthioformimidoyl)phenyl)acetyl]-β-alanyl]-3-t-butoxycarbonyl-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide, m.p. 103-104°C (acetone/diethyl ether), after crystallisation.

d) Reaction of 90 mg of the precursor with ammonium acetate as described in Example 1f) gives 62 mg of N-[N-[N-(p-amidinophenylacetyl)-β-alanyl]-3-t-butoxycarbonyl-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide, m.p. 152°C (methanol/diethyl ether).

Example 4

By treatment of 55 mg of N-[N-[4-(p-amidinophenylcarbamoyl)butyryl]-3-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide with trifluoroacetic acid as described in Example 1, 31 mg of N-[N-[4-(p-amidinophenylcarbamoyl)butyryl]-L-α-aspartyl]-3-phenyl-L-alanine trifluoroacetate (5:4), m.p. 159-161°C, are obtained after crystallisation from ethanol/diethyl ether.

The starting material can be prepared as follows:

a) By coupling 1.18 g of 4-aminobenzonitrile with 1.25 ml of monomethyl glutarate as described in Example 1a), 1.83 g of methyl 4-[(p-cyanophenyl)carbamoyl]-butyrate, m.p. 126-127°C, are obtained after recrystallisation from ethyl acetate.

b) 6 ml of 1N sodium hydroxide solution is added to a solution of 1 g of the precursor in 10 ml of methanol. After 7 hours, the reaction mixture is concentrated, the residue is extracted with ethyl acetate and the extract is then neutralised using 1N hydrochloric acid. The

resulting precipitate is filtered off, washed with water and dried. 575 mg of 4-[(p-cyanophenyl)carbamoyl]butyric acid, m.p. 200-201°C, are obtained.

c) By coupling 464 mg of the precursor with 863 mg of H-Asp(O-tBu)-Phe-O-tBu as described in Example 1a), 701 mg of N-[3-(t-butoxycarbonyl)-N-[4-(p-cyanophenylcarbamoyl)butyryl]-L-alanyl]-3-phenyl-L-alanine t-butyl ester, m.p. 64-66°C, are obtained after chromatography on silica gel using ethyl acetate and subsequent stirring in hexane.

d) Reaction of 350 mg of the precursor with hydrogen sulphide in analogy to Example 1d) yields 304 mg of N-[3-(t-butoxycarbonyl)-N-[4-(p-thiocarbamoylphenyl)-butyryl]-L-alanyl]-3-phenyl-L-alanine t-butyl ester, m.p. 178-179°C, after recrystallisation from ethyl acetate.

e) Methylation of 150 mg of the precursor in analogy to Example 1e) gives 175 mg of N-[3-(t-butoxycarbonyl)-N-[4-[[p-(1-(methylthio)formimidoyl]phenyl]carbamoyl]-butyryl]-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide (1:1), m.p. 127-128°C, after crystallisation using diethyl ether.

f) 60 mg of N-[N-[4-(p-amidinophenylcarbamoyl)butyryl]-3-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide, m.p. 130-132°C, are obtained from 90 mg of the precursor in analogy to Example 1f).

Example 5

Reaction of 100 mg of N-[N-[(p-amidinophenethylcarbamoyl)acetyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide with trifluoroacetic acid as described in Example 1 gives 69 mg of N-[N-[(p-amidinophenethylcarbamoyl)acetyl]-L-α-aspartyl]-3-phenyl-L-alanine trifluoroacetate, m.p. 141-143°C, after crystallisation using diethyl ether.

The starting material can be prepared as follows:

a) 370 mg of p-(2-aminoethyl)benzonitrile, MS: 147 $(M+H)^+$, are obtained from 876 mg of p-cyanohydrocinnamic acid (Pharmazie 28, 1973, 724) by a known reaction sequence (Organic Synthesis 51, 1971, 46).

b) A solution of 0.59 ml of methyl malonyl chloride in 5 ml of THF is added dropwise at -10°C to a solution of 731 mg of p-(2-aminoethyl)benzonitrile and 1.39 ml of triethylamine in 10 ml of THF. The mixture is then allowed to warm to room temperature, and is poured into ice-water and adjusted to pH 2 with 1N hydrochloric acid. The THF is evaporated and the aqueous extracts are extracted with ethyl acetate. After drying and concentrating, 380 mg of methyl (p-cyanophenethyl)malonamate, m.p. 125°C, are obtained.

c) Analogously to Example 4b), hydrolysis of 750 mg of the product from b) gives 365 mg of N-(p-cyanophenethyl)-malonamic acid, m.p. 137-139°C.

d) Analogously to Example 1a), 352 mg of N-[3-(t-butoxycarbonyl)-N-[(p-cyanophenethylcarbamoyl)acetyl]-L-alanyl]-3-phenyl-L-alanine t-butyl ester, MS: 607 $(M-H)^-$, is obtained by coupling 300 mg of the precursor with 507 mg of H-Asp(O-tBu)-Phe-O-tBu after chromatography on silica gel using ethyl acetate.

e) Analogously to Examples 1d), e) and f), the same reaction sequence using 380 mg of the product from d) yields 152 mg of N-[N-[(p-amidinophenethylcarbamoyl)-acetyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanine t-butyl ester hydroiodide, m.p. 91-93°C (decomposition), after crystallisation using diisopropyl ether.

Example 6

119 mg of the trifluoracetate of N-[N-[4-(p-amidinobenzamido)butyryl]-L-α-aspartyl]-L-valine, m.p. 174°C (decomposition), are obtained in analogy to Example 1 from 200 mg of N-[N-[4-(p-amidinobenzamido)-butyryl]-3-(t-butoxycarbonyl)-L-alanyl]-L-valine t-butyl ester hydroiodide after recrystallisation from ethanol/diethyl ether.

The starting material can be prepared as follows:

a) By coupling 783 mg of Z-4-aminobutyric acid with 1 g of H-Asp(O-tBu)-Val-O-tBu (obtained from the condensation of Z-Asp(O-tBu)-OH with H-Val-O-tBu followed by hydrogenolysis) as described in Example 1a), 1.17 g of N-[N-[4-[1-(benzyloxy)formamido]butyramido]-3-(t-butoxy-

carbonyl)-L-alanyl]-L-valine t-butyl ester, m.p. 64-65°C, are obtained after chromatography on silica gel using ethyl acetate and crystallisation using hexane.

b) Hydrogenolysis of 1.1 g of the precursor analogously to Example 1b) gives 1 g of N-[N-(4-aminobutyryl)-3-(t-butoxycarbonyl)-L-alanyl]-L-valine t-butyl ester, m.p. 99-100°C.

c) A solution of 859 mg of the product from b) is added, after 2 hours at 0°C, to a solution of 324 mg of 4-cyanobenzoic acid, 352 mg of 2-chloro-4,6-dimethoxy-1,3,5-triazine and 0.24 ml of N-methylmorpholine in 10 ml of dimethylformamide. The mixture is allowed to warm to room temperature and 772 mg of N-[N-[4-(p-cyanobenzamido)butyryl]-3-(t-butoxycarbonyl)-L-alanyl]-L-valine t-butyl ester, MS: 559 $(M+H)^+$, are obtained after working up as in Example 1d) and after chromatography on silica gel using ethyl acetate.

d) If 760 mg of the product from c) are subjected to the same reaction sequence as described in Examples 1d), e) and f), 444 mg of N-[N-[4-(p-amidinobenzamido)-butyryl]-3-(t-butoxycarbonyl)-L-alanyl-L-valine t-butyl ester hydroiodide, m.p. 105-107°C (decomposition) are obtained after crystallisation using diisopropyl ether.

Example 7

1.09 g of rac-N-1-[[[p-[N-(benzyloxycarbonyl)-amidino]benzoyl]-3-piperidinyl]carbonyl]-β-alanine benzyl ester and 0.25 g of Pd/C are stirred in 20 ml of acetic acid under hydrogen. The catalyst is filtered off and the filtrate is evaporated. The residue is taken up in water and the solution is evaporated. The precipitate is suspended in methanol, adjusted to pH 8 with ammonia and stirred, then filtered with suction, washed with methanol and dried. 530 mg of rac-N-[[1-(p-amidinobenzoyl)-3-piperidinyl]carbonyl]-β-alanine are obtained in the form of the hydrate (2:1), m.p. >265°C, MS: 347 (96, M-H).

The starting material can be prepared as follows:

a) rac-N-(t-butoxycarbonyl)piperidine-3-carboxylic acid (Can. J. Physiol. Pharmacol. 57, 1979, 763) in THF is

activated with chlorodimethoxytriazine and N-methylmorpholine and then coupled with β-alanine benzyl ester p-toluenesulphonate (J. Org. Chem. 17, 1952, 1564) and N-methylmorpholine to give rac-N-[[1-(t-butoxycarbonyl)-3-piperidinyl]carbonyl]-β-alanine benzyl ester, m.p. 57-59°C.

b) By cleavage with trifluoroacetic acid, the trifluoroacetate of rac-(3-piperidinylcarbonyl)-β-alanine benzyl ester is obtained therefrom.

c) This is reacted in methylene chloride/aqueous sodium bicarbonate solution with p-amidinobenzoyl chloride and then with benzyl chloroformate in the presence of sodium carbonate to give rac-N-1-[[[p-[N-(benzyloxycarbonyl)-amidino]benzoyl]-3-piperidinyl]carbonyl]-β-alanine benzyl ester, MS: 571 (10, M-H).

Example 8

512 mg of N-[4-[p-[N-(benzyloxycarbonyl)amidino]-benzamido]butyryl]-β-alanine benzyl ester and 170 mg of Pd/C in 10 ml of acetic acid are stirred under hydrogen. The catalyst is filtered off and the filtrate is evaporated. The residue is dissolved in water and the solution is evaporated. The residue is suspended in water, adjusted to pH 7 using ammonia, filtered with suction, washed with water and dried. 239 mg of N-[4-(p-amidinobenzamido)butyryl]-β-alanine, m.p. >250°C, MS: 321 (12, M+H), are obtained.

The starting material can be prepared as follows:

a) 4-(t-Butoxycarbonylamino)butyric acid in THF is activated with chlorodimethoxytriazine and N-methylmorpholine and reacted with β-alanine benzyl ester p-toluenesulphonate in the presence of N-methylmorpholine to give N-[4-(1-t-butoxyformamido)butyryl]-β-alanine benzyl ester. m.p. 54-55°C.

b) From this in trifluoroacetic acid, the trifluoroacetate of N-(4-aminobutyryl)-β-alanine benzyl ester is obtained.

c) The latter is reacted in methylene chloride/water/sodium hydrogen carbonate with p-amidinobenzoyl chloride and then with benzyl chloroformate in the presence of

sodium carbonate to give N-[4-(p-[N-(benzyloxycarbonyl)-amidino]benzamido)butyryl]-β-alanine benzyl ester, m.p. 173-183°C.

Example 9

Analogously to Example 8, N-[N-(p-amidinobenzoyl)-β-alanyl]-β-alanine, m.p. >250°C, MS: 307 (6, M-H), is obtained in the form of the hydrate (2:1) from N-[N-[p-[N-(benzyloxycarbonyl)amidino]benzoyl]-β-alanyl]-β-alanine benzyl ester.

The starting material can be prepared as follows:

a) N-(t-butoxycarbonyl)-β-alanine and β-alanine benzyl ester are coupled analogously to the above examples to give N-[N-(t-butoxycarbonyl)-β-alanyl]-β-alanine benzyl ester, mp. 84-85°C.

b) The trifluoroacetate of (β-alanyl)-β-alanine benzyl ester is obtained therefrom in trifluoroacetic acid.

c) This is reacted with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give N-[N-[p-[N-(benzyloxycarbonyl)amidino]benzoyl]-β-alanyl]-β-alanine benzyl ester, m.p. 165-166°C.

Example 10

In analogy to Example 8, N-[(DL)-N-(p-amidinobenzoyl)-3-phenyl-β-alanyl]-β-alanine is obtained as the hydrate (3:1), m.p. >250°C, MS: 383 (62, M+H), from N-[(DL)-N-[p-[N-(benzyloxycarbonyl)amidino]benzoyl]-3-phenyl-β-alanyl]-β-alanine benzyl ester.

The starting material can be prepared as follows:

a) DL-N-(t-butoxycarbonyl)-3-phenyl-β-alanine and β-alanine benzyl ester are coupled analogously to the above examples to give N-[(DL)-N-(t-butoxycarbonyl)-3-phenyl-β-alanyl]-β-alanine benzyl ester, m.p. 143-144°C.

b) The trifluoroacetate of [(DL)-3-phenyl-β-alanyl]-β-alanine benzyl ester is obtained therefrom in trifluoroacetic acid.

c) This is reacted with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give N-[(DL)-N-[p-[N-(benzyloxycarbonyl)amidino]benzoyl]-3-phenyl-β-alanyl-β-alanine benzyl ester, m.p. 187-189°C.

Example 11

443 mg of N-[3-[(benzyloxy)carbonyl]-N-[5-[p-[N-[(benzyloxy)carbonyl]amidino]benzamido]valeryl]-L-alanyl]-3-phenyl-L-alanine benzyl ester and 111 mg of Pd/C in 9 ml of acetic acid are stirred under hydrogen gas for 3½ hours. The solution is filtered and evaporated, the residue is dissolved in water and the solution is again evaporated. The residue is stirred in water, filtered off with suction and dried. 246 mg of N-[N-[5-(p-amidinobenzamido)valeryl]-L-α-aspartyl]-3-phenyl-L-alanine, m.p. 241°C, are obtained as the hydrate (1:2).

The starting ester, m.p. 169-171°C, can be prepared as follows:

a) N-(t-butoxycarbonyl)-L-aspartic acid 4-benzyl ester is coupled with 3-phenyl-L-alanine benzyl ester to give N-[3-[(benzyloxy)carbonyl]-N-(t-butoxycarbonyl)-L-alanyl]-3-phenyl-L-alanine benzyl ester, m.p. 93-94°C.

b) This is deprotected using trifluoroacetic acid and coupled with 5-(1-t-butoxyformamido)valeric acid to give N-[3-[(benzyloxy)carbonyl]-N-[5-(1-t-butoxyformamido)-valeryl]-L-alanyl]-3-phenyl-L-alanine benzyl ester, m.p. 119.5-120.5°C.

c) The latter is freed of the t-butoxycarbonyl protecting group in trifluoroacetic acid and then converted into the starting material in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate.

Example 12

Analogously to Example 11, N,N'-[[(S)-(p-amidinobenzamido)ethylene]dicarbonyl]di-β-alanine, m.p. >250°C, is obtained from N,N'-[[(S)-[p [N-[(benzyloxy)carbonyl]-amidino]benzamido]ethylene]dicarbonyl]-di-β-alanine dibenzyl diester after evaporating with water and stirring with methanol.

The starting ester, m.p. 171-172°C, is obtained as follows:

a) N-(t-butoxycarbonyl)-L-aspartic acid is coupled with two equivalents of β-alanine benzyl ester to give N,N'-[[(S)-(1-t-butoxyformamido)ethylene]dicarbonyl]di-β-

alanine dibenzyl ester, m.p. 109-110°C.

b) After cleavage of the t-butoxycarbonyl group with trifluoroacetic acid, the product is reacted in methylene chloride/aqueous sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester.

Example 13

Analogously to Example 11, 2-N-(p-amidinobenzoyl)-4-N-(2-carboxyethyl)-L-asparagine, m.p. 212°C (dec.) is obtained from N-[(S)-N-[p-[N-[(benzyloxy)carbonyl]amidino]benzoyl]-3-[(benzyloxy)carbonyl]-β-alanyl]-β-alanine benzyl ester.

The starting ester is obtained as follows:

a) N-(t-butoxycarbonyl)-L-aspartic acid 1-benzyl ester is coupled with β-alanine benzyl ester to give 3-[[2-(benzyloxy)carbonyl]ethyl]carbamoyl]-N-(t-butoxycarbonyl)-L-alanine benzyl ester, m.p. 77-78°C.

b) After cleavage of the t-butoxycarbonyl protecting group in trifluoroacetic acid, the product is coupled in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently reacted with benzyl chloroformate to give the starting ester, m.p. 122-123°C.

Example 14

Analogously to Example 8, N-[5-(p-amidinobenzamido)valeryl]-β-alanine, m.p. >280°C, is obtained from N-[5-[p-[N-[(benzyloxy)carbonyl]amidino]benzamido]-valeryl]-β-alanine benzyl ester.

The starting ester can be prepared as follows:

a) 5-(1-t-butoxyformamido)valeric acid is coupled with β-alanine benzyl ester to give N-[5-(1-t-butoxyformamido)valeryl]-β-alanine benzyl ester, m.p. 69-70°C.

b) The trifluoroacetate of N-(5-aminovaleryl)-β-alanine benzyl ester is obtained therefrom in trifluoroacetic acid.

c) This is reacted in methylene chloride/water in the presence of sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester, m.p. 161-161.5°C.

Example 15

704 mg of rac-N-[[1-[3-[1-[(E/Z))-N,N'-bis-(t-benzyl ester and 176 mg of Pd/C in 14.1 ml of formic acid are stirred under hydrogen for 13 hours. The catalyst is filtered off and washed with 1:1 formic acid/water. The filtrate is evaporated, the residue is dissolved in water and the solution is again evaporated. The residue is chromatographed using ethanol/methanol on silica gel. 254 mg of rac-N-[[1-[3-(1-amidino-4-piperidinyl)propionyl]-3-piperidinyl]carbonyl]-β-alanine, MS: 382 (100, M-H), are obtained.

The starting ester can be prepared as follows:

a) 4-Piperidinopropionic acid is reacted with N,N'-bis(t-butoxycarbonyl)-S-methylisothiourea in t-butanol and 2N sodium hydroxide solution to give 3-[1-[(E/Z)-N,N'-bis(t-butoxycarbonyl)amidino]-4-piperidinyl]-propionic acid.

b) This is coupled with rac-N-(3-piperidinylcarbonyl)-β-alanine benzyl ester to give the starting ester, MS: 672 (12, M+H).

Example 16

115 mg of N-[[(S)-1-[p-[N-[(benzyloxy)carbonyl]-amidino]benzoyl]-2-pyrrolidinyl]acetyl]-β-alanine and 50 mg of Pd/C are stirred under hydrogen for 4 hours in 2.5 ml of acetic acid. The catalyst is filtered off and the solution is evaporated. The residue is dissolved in water, evaporated again and chromatographed on silica gel using methanol. 46 mg of N-[[(S)-1-(p-amidinobenzoyl)-2-pyrrolidinyl]acetyl]-β-alanine, m.p. >250°C, are obtained.

The starting ester can be prepared as follows:

a) (S)-1-[(Benzyloxy)carbonyl]-2-pyrrolidineacetic acid is coupled with β-alanine t-butyl ester to give N-[[(S)-1-[(benzyloxy)carbonyl]-2-pyrrolidinyl]acetyl]-β-alanine t-butyl ester, MS: 391 (69, M+H).

b) The acetate of N-[(2-pyrrolidinyl)acetyl]-β-alanine t-butyl ester is obtained therefrom by hydrogenation in acetic acid.

c) This is reacted in methylene chloride/water in the

presence of sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give N-[[(S)-1-[p-[N-[(benzyloxy)carbonyl]amidino]-benzoyl]-2-pyrrolidinyl]acetyl]-β-alanine t-butyl ester, m.p. 127-128°C.

d) The starting ester, MS: 481 (100, M+H), is obtained therefrom in formic acid.

Example 17

300 mg of benzyl-(S)-3-[[N-[p-[N-(t-butoxycarbonyl)amidino]benzoyl]-β-alanyl]amino]-3-[(p-methoxyphenethyl)carbamoyl]propionate and 75 mg of Pd/C are stirred under hydrogen for 4½ hours in 6 ml of formic acid. The catalyst is filtered off, the filtrate is evaporated, the residue is taken up in water and the solution is evaporated again. The crystalline substance is suspended in water, adjusted to pH 8 while stirring with ammonia and then filtered with suction. 151 mg of (S)-3-[[N-(p-amidinobenzoyl)-β-alanyl]amino-3-[(p-methoxyphenethyl)carbamoyl]-propionic acid is obtained as the hydrate (1:1), m.p. 217°C.

The starting ester can be obtained as follows:

a) β-Alanine benzyl ester is reacted in methylene chloride/water sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with di-t-butyl dicarbonate and sodium carbonate to give N-[p-[N-(t-butoxycarbonyl)-amidino]benzoyl]-β-alanine benzyl ester, m.p. 127-128°C.

b) N-[p-[N-(t-butoxycarbonyl)amidino]benzoyl]-β-alanine, MS: 336 (21, M-H), is obtained therefrom by catalytic hydrogenation.

c) N-(t-butoxycarbonyl)aspartic acid 4-benzyl ester is coupled with 2-(4-methoxyphenyl)ethylamine to t-butyl-[(S)-2-[(benzyloxy)carbonyl]-1-[(p-methoxyphenethyl)-carbamoyl]ethyl]carbamate, m.p. 103-104°C.

d) From this in trifluoroacetic acid is obtained the trifluoroacetate of 3-[(p-methoxyphenethyl)carbamoyl]-β-alanine benzyl ester.

e) The latter is coupled with the product described in b) to give the starting ester, m.p. 150°C (dec.).

Example 18

Analogously to Example 6, N-[N-[N-(p-amidinobenzoyl)-β-alanyl]-L-α-aspartyl]-L-leucine isopropyl ester is obtained as the hydrate (1:1.3), m.p. 234°C (dec.), from N-[3-[(benzyloxycarbonyl]-N-[N-[p-[N-[(benzyloxy)carbonyl]amidino]benzoyl]-β-alanyl]-L-alanyl]-L-leucine isopropyl ester.

The starting ester can be obtained in the following way:

a) N-(t-butoxycarbonyl)-L-leucine is converted into N-(t-butoxycarbonyl)-L-leucine isopropyl ester, $[\alpha]_D$ = -33° (MeOH, c = 0.5), using dicyclohexylcarbodiimide, p-toluenesulphonic acid and isopropanol in pyridine.

b) The trifluoroacetate of L-leucine isopropyl ester is obtained therefrom in trifluoroacetic acid.

c) This is coupled with N-(t-butoxycarbonyl)-L-aspartic acid 4-benzyl ester to give N-[3-[(benzyloxy)carbonyl]-N-(t-butoxycarbonyl)-L-alanyl]-L-leucine isopropyl ester, MS: 479 (25, M+H).

d) After cleavage of the t-butoxycarbonyl protecting group and coupling with N-(t-butoxycarbonyl)-β-alanine, N-[3-[(benzyloxy)carbonyl]-N-[N-(t-butoxycarbonyl)-β-alanyl]-L-alanyl]-L-leucine isopropyl ester, m.p. 103-104°C, is obtained therefrom.

e) This is freed of the t-butoxycarbonyl protecting group in trifluoroacetic acid and then converted into the starting ester in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently using benzyl chloroformate, m.p. 176-177°C.

Example 19

Analogously to Example 8, N-[[(R)-1-(p-amidinobenzoyl)-3-pyrrolidinyl]carbonyl]-β-alanine is obtained as the hydrate (4:3), m.p. >250°C, $[\alpha]_D$ = -4.13° (1N HCl, c = 0.46%), from N-[[(R)-1-[p-[N-[(benzyloxy)carbonyl]-amidino]benzoyl]-3-pyrrolidinyl]carbonyl]-β-alanine benzyl ester.

The starting ester can be prepared in the following manner:

a) (R)-1-[(R)-α-methylbenzyl]-3-pyrrolidinomethanol, di-t-butyl dicarbonate and Pd/C in ethanol are stirred under hydrogen for 20 hours. t-Butyl (R)-3-(hydroxymethyl)-1-pyrrolidinocarboxylate, m.p. 35°C, $[\alpha]_D$ = -19.5° (methanol, c = 1.0), is obtained.

b) From this, (R)-1-(t-butoxycarbonyl)-3-pyrrolidinocarboxylic acid, m.p. 135-138°C, $[\alpha]_D$ = -15° (MeOH, c = 1.0), is obtained using pyridinium dichromate in DMF.

c) This is coupled with β-alanine benzyl ester to give N-[[(R)-1-(t-butoxycarbonyl)-3-pyrrolidinyl]carbonyl]-β-alanine benzyl ester, m.p. 83-84°C, $[\alpha]_D$ = -3.4° (MeOH, c = 1.0).

d) The trifluoroacetate of N-[[(R)-3-pyrrolidinyl]-carbonyl]-β-alanine benzyl ester is obtained therefrom in trifluoroacetic acid.

e) This is reacted in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester, $[\alpha]_D$ = -2.2° (MeOH, c = 0.5).

Example 20

Analogously to Example 16, N-[N-(p-amidinobenzoyl)-2-methyl-β-alanyl]-L-α-aspartamide (2:1 epimers), m.p. 280°C, is obtained from benzyl (S)-3-[[D/L-N-[p-[N-[(benzyloxy)carbonyl]amidino]benzoyl]-2-methyl-β-alanyl]amino]succinamate.

The starting ester can be prepared as follows:

a) Benzyl (S)-3-(1-t-butoxyformamido)succinamate is deprotected using trifluoroacetic acid and then coupled with DL-N-(t-butoxycarbonyl)-2-methyl-β-alanine. t-Butyl [(RS)-2-[[(S)-2-[(benzyloxy)carbonyl]-1-carbamoylethyl]-carbamoyl]propyl]carbamate, m.p. 135-136°C, is obtained.

b) After cleavage of the t-butoxycarbonyl protecting group in trifluoroacetic acid, the product is coupled in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and finally reacted with benzyl chloroformate to give the starting ester (2:1 epimers), m.p. 178.5-179.5°C.

Example 21

548 mg of N-[N-[p-[N-(t-butoxycarbonyl)amidino]-

phenyl]acetyl]-β-alanyl]-β-alanine benzyl ester are allowed to stand in 11 ml of formic acid for 18 hours. After addition of 137 mg of Pd/C, the mixture is stirred under hydrogen for 4 hours. The catalyst is filtered off and the filtrate is evaporated. The residue is dissolved in water and the solution is evaporated again. The residue is suspended in water and adjusted to pH 8 using ammonia, then filtered with suction and dried. 290 mg of N-[N-[(p-amidinophenyl)acetyl]-β-alanyl]-β-alanine are obtained as the hydrate (1:1), m.p. 286°C (dec.).

The starting material, m.p. 262°C (dec.), is obtained by reaction of N-(β-alanyl)-β-alanine benzyl ester in DMF/triethylamine with p-amidinophenylacetyl chloride and subsequent reaction with di-t-butyl dicarbonate.

Example 22

535 mg of rac-N-[[1-[p-[N-(t-butoxycarbonyl)-amidino]phenylacetyl]-3-piperidinyl]carbonyl]-β-alanine benzyl ester are allowed to stand in 11 ml of formic acid for 19 hours. The solvent is evaporated, and the residue is evaporated with water and recrystallised from acetonitrile. 340 mg of rac-N-[[[1-(p-amidinophenyl)acetyl]-3-piperidinyl]carbonyl]-β-alanine benzyl ester formate (1:1), m.p. 97-98°C, are obtained.

The starting ester, MS: 551 (9, M-H), is obtained by coupling rac-N-[(3-piperidinyl)carbonyl]-β-alanine benzyl ester in DMF/triethylamine with p-amidinophenylacetyl chloride and subsequent reaction with di-t-butyl dicarbonate.

Example 23

535 mg of rac-N-[[1-[p-[N-(t-butoxycarbonyl)-amidino]phenylacetyl]-3-piperidinyl]carbonyl]-β-alanine benzyl ester are allowed to stand in 11 ml of formic acid for 19 hours, and the mixture is treated with 134 mg of Pd/C and stirred under hydrogen for 4 hours. The solution is filtered and evaporated, the residue is dissolved in water and the solution is evaporated again. The product is stirred in acetonitrile, filtered with suction and dried. 272 mg of rac-N-[[1-[(p-amidinophenyl)acetyl]-

3-piperidinyl]carbonyl]-β-alanine, MS: 361 (4), M+H+, are obtained.

Example 24

1127 mg of N-[3-[(benzyloxy)carbonyl]-N-[N-[3-[1-[(E or Z)-N,N'-bis(t-butoxycarbonyl)amidino]-4-piperidinyl]propionyl]-β-alanyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester are allowed to stand in 22.5 ml of formic acid for 21 hours. After addition of 282 mg of Pd/C, the mixture is stirred under hydrogen for 5 hours. The solution is filtered and evaporated, the residue is dissolved in water and the solution is evaporated again. The residue is stirred in water, filtered with suction and dried. 543 mg of N-[N-[N-[3-(1-amidino-4-piperidinyl)propionyl]-β-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine, m.p. 246°C (dec.), are obtained.

The starting ester can be prepared as follows:

a) N-(t-butoxycarbonyl)-β-alanine is coupled with N-[3-[(benzyloxy)carbonyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester to give N-[3-[(benzyloxy)carbonyl]-N-[N-(t-butoxycarbonyl)-β-alanyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester, m.p. 124-125°C.

b) After cleavage of the t-butoxycarbonyl protecting group, the product is coupled with 3-[1-[N,N'-bis-(t-butoxycarbonyl)amidino]-4-piperidinyl]propionic acid to give the starting ester, 1:1 ethyl acetate solvate, m.p. 100°C (dec.).

Example 25

1.3 g of 3-[(benzyloxy)carbonyl]-N-[5-[p-[N-[(benzyloxy)carbonyl]amidino]benzamido]valeryl]-L-alanine isobutyl ester and 325 mg of Pd/C in 25 ml of acetic acid are stirred under hydrogen for 5½ hours. The solution is filtered and evaporated and the residue is evaporated successively with water, methanol and ethanol. The product is adjusted to pH 8 in acetonitrile using ammonia, stirred and filtered with suction. 596 mg of isobutyl N-[5-(p-amidinobenzamido)valeryl]-L-α-aspartate are obtained as the hydrate (1:1), m.p. 162-166°C.

The starting ester, m.p. 127.5-129.5°C, can be prepared as follows:

a) Benzyl N-(t-butoxycarbonyl)-L-α-aspartate is converted into the N-(t-butoxycarbonyl)-3-[(benzyloxy)-carbonyl]-L-alanine isobutyl estet, MS: 323 (9, M-C_4H_9), using dicyclohexylcarbodiimide, p-toluenesulphonic acid and isobutyl alcohol in pyridine.

b) After cleavage of the t-butoxycarbonyl group in trifluoroacetic acid, the product is coupled with 5-(1-t-butoxyformamido)valeric acid to give 3-[(benzyloxy)-carbonyl]-N-[5-(1-t-butoxyformamido)valeryl]-L-alanine isobutyl ester, m.p. 64-66°C.

c) This is deprotected using trifluoroacetic acid and then reacted in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester.

Example 26

562 mg of benzyl (S)-β-[[DL-N-[p-[N-[(benzyloxy)-carbonyl]amidino]benzoyl]-3-methyl-β-alanyl]amino]-γ-oxo-1-pyrrolidinobutyrate and 140 mg of Pd/C in 11 ml of acetic acid are stirred under hydrogen for 2 hours. The filtered solution is evaporated and the residue is evaporated successively with water, methanol and ethanol. The residue is finally adjusted to pH 8 in ethanol using ammonia, stirred and filtered off with suction. 289 mg of (S)-β-[[DL-N-(p-amidinobenzoyl)-3-methyl-β-alanyl]amino]-γ-oxo-1-pyrrolidinobutyric acid are obtained as the hydrate (2:3), m.p. 222-224°C.

The starting ester can be prepared in the following way:

a) Benzyl (S)-β-(1-t-butoxyformamido)-γ-oxo-1-pyrrolidinobutyrate is deprotected using trifluoroacetic acid and coupled with (RS)-3-(1-t-butoxyformamido)butyric acid to give benzyl (S)-β-[(RS)-3-(1-t-butoxyformamido)-butyramido]-γ-oxo-1-pyrrolidinobutyrate, m.p. 104-105°C.

b) From this, the starting ester, MS: 642 (100, M-H), is obtained after cleavage of the t-butoxycarbonyl group in trifluoroacetic acid and reaction with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate in methylene chloride/water/sodium bicarbonate.

Example 27

Analogously to Example 8, DL-N-[N-(p-amidinobenzoyl)-β-alanyl]-3-methyl-β-alanine is obtained as the hydrate (3:1) m.p. 291°C (dec.), from DL-N-[N-[p-[N-[(benzyloxy)carbonyl]amidino]benzoyl]-β-alanyl]-3-methyl-β-alanine benzyl ester.

The starting ester, m.p. 179-180°C, can be prepared as follows:

a) N-(t-butoxycarbonyl)-β-alanine is coupled with DL-3-aminobutyric acid benzyl ester to give DL-N-[N-(t-butoxycarbonyl)-β-alanyl]-3-methyl-β-alanine benzyl ester, m.p. 70-72°C.

b) DL-N-(β-alanyl)-3-methyl-β-alanine benzyl ester is obtained therefrom using trifluoroacetic acid.

c) This is reacted in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester.

Example 28

Analogously to Example 8, N-[N-[N-(p-amidinobenzoyl)-β-alanyl]-L-α-aspartyl]-L-serine ethyl ester is obtained as the hydrate (2:7), m.p. 201-203°C, from N-[3-[(benzyloxy)carbonyl]-N-[N-[p-[N-[(benzyloxy)carbonyl]-amidino]benzoyl]-β-alanyl]-L-serine ethyl ester.

The starting ester, m.p. 177-179°C, can be prepared as follows:

a) Benzyl N-(t-butoxycarbonyl)-L-α-aspartate is coupled with L-serine ethyl ester to give N-[3-[(benzyloxy)carbonyl]-N-(t-butoxycarbonyl)-L-alanyl]-L-serine ethyl ester, m.p. 96-97°C.

b) After cleavage of the t-butoxycarbonyl group, the product is coupled with N-(t-butoxycarbonyl)-β-alanine to give N-[3-[(benzyloxy)carbonyl]-N-[N-(t-butoxycarbonyl)-β-alanyl]-L-alanyl]-L-serine ethyl ester, m.p. 132-134°C.

c) This is deprotected in trifluoroacetic acid and the product is subsequently reacted in methylene chloride/-water/sodium bicarbonate with p-amidinobenzoyl chloride and finally with benzyl chloroformate to give the starting ester.

Example 29

Analogously to Example 8, N-[DL-N-(p-amidinobenzoyl)-2-phenyl-β-alanyl]-β-alanine is obtained as the hydrate (4:1), m.p. 276°C, from N-[N-[p-[DL-N-[(benzyloxy)carbonyl]amidino]benzoyl]-2-phenyl-β-alanyl]-β-alanine benzyl ester.

The starting ester, m.p. 173-174°C, is prepared as follows:

a) DL-2-phenyl-β-alanine is reacted with di-t-butyl dicarbonate in t-butanol and sodium hydroxide solution to give DL-N-(t-butoxycarbonyl)-2-phenyl-β-alanine, m.p. 147-148°C.

b) This is coupled with β-alanine benzyl ester to give N-[DL-N-(t-butoxycarbonyl)-2-phenyl-β-alanyl]-β-alanine benzyl ester, m.p. 115-116°C.

c) After cleavage of the protecting group, the product is reacted in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester.

Example 30

Analogously to Example 8, DL-N-[N-(p-amidinobenzoyl)-β-alanyl]-2-methyl-β-alanine is obtained as the hydrate (3:1), m.p. >300°C, from N-[N-[p-[N-[(benzyloxy)carbonyl]amidino]benzoyl]-β-alanyl]-DL-2-methyl-β-alanine benzyl ester.

The starting ester, m.p. 159-160°C, is obtained as follows:

a) N-(t-butoxycarbonyl)-β-alanine is coupled with DL-2-methyl-β-alanine benzyl ester to give DL-N-[N-(t-butoxycarbonyl)-β-alanyl]-2-methyl-β-alanine benzyl ester, MS: 365 (47, M+H).

b) After cleavage of the protecting group, the product is reacted in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester.

Example 31

Analogously to Example 11, N-[N-[[(R)-1-(p-amidinobenzoyl)-3-pyrrolidinyl]carbonyl]-L-α-aspartyl]-3-phenyl-L-alanine acetate (2:1) is obtained as the

hydrate (3:2), m.p. 215°C, from N-[N-[[(R)-1-[p-[N-[(benzyloxy)carbonyl]amidino]benzoyl]-3-pyrrolidinyl]-carbonyl]-3-[(benzyloxy)carbonyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester after evaporating with water and stirring in ethanol.

The starting ester is obtained as follows:

a) (R)-1-(t-butoxycarbonyl)-3-pyrrolidinocarboxylic acid is coupled with N-[3-[(benzyloxy)carbonyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester to give N-[N-[[(R)-1-(t-butoxycarbonyl)-3-pyrrolidinyl]carbonyl]-3-[(benzyloxy)carbonyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester, m.p. 84-85°C.

b) After removal of the t-butoxycarbonyl group in trifluoroacetic acid, the product is reacted in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester, m.p. 144-145°C.

Example 32

Analogously to Example 7, DL-N-[N-(p-amidinobenzoyl)-β-alanyl]-2-phenyl-β-alanine is obtained as the hydrate (1:1), m.p. 243-245°C, from N-[N-[p-[N-[(benzyloxy)carbonyl]amidino]benzoyl]-β-alanyl]-DL-2-phenyl-β-alanine benzyl ester.

The starting ester can be obtained as follows:

a) N-(t-butoxycarbonyl)-2-phenyl-β-alanine is heated to reflux in acetone with benzyl bromide and potassium carbonate for 17 hours. DL-N-(t-butoxycarbonyl)-2-phenyl-β-alanine benzyl ester, m.p. 58-59°C, is obtained.

b) After cleavage of the t-butoxycarbonyl group, the product is coupled with N-(t-butoxycarbonyl)-β-alanine to give DL-N-[N-(t-butoxycarbonyl)-β-alanyl]-2-phenyl-β-alanine benzyl ester, m.p. 84.5-86°C.

c) This is converted into the trifluoroacetate of the -(β-alanyl)-2-phenyl-β-alanine benzyl ester in trifluoroacetic acid.

d) The latter is reacted in methylene chloride/water/-sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester, m.p. 165-166°C.

Example 33

Analogously to Example 11, p-[2-[[N-[N-(p-amidinobenzoyl)-β-alanyl]-L-α-asparty]amino]ethyl]-benzoic acid is obtained as the hydrate (3:7), m.p. 194-196°C (methanol/water), from benzyl p-[2-[[3-[(benzyloxy)carbonyl]-N-[N-[p-[N-[(benzyloxy)carbonyl]amidino]-benzoyl]-β-alanyl]-L-alanyl]amino]ethyl]benzoate.

The starting ester, m.p. 162-163°C, can be prepared as follows:

a) p-(2-chloroethyl)benzoyl chloride is converted into benzyl p-(2-chloroethyl)benzoate, MS: 274 (8, M), using benzyl alcohol and pyridine in methylene chloride.

b) Benzyl p-(2-azidoethyl)benzoate, MS: 281 (2, M) is obtained therefrom using sodium azide in DMSO.

c) This is reacted in pyridine with triphenylphosphine and subsequently with conc. ammonia to give benzyl p-(2-aminoethyl)-benzoate, MS: 226 (16, M-CH_2NH).

d) Benzyl p-[2-[[3-[(benzyloxy)carbonyl]-N-(t-butoxycarbonyl)-L-alanyl]amino]-ethyl]benzoate, m.p. 99-100°C, is obtained therefrom by coupling with benzyl N-(t-butoxycarbonyl)-L-α-aspartate.

e) This is deprotected in trifluoroacetic acid and coupled with N-(t-butoxycarbonyl)-β-alanine to give p-[2-[[3-[(benzyloxy)-carbonyl]-N-[N-(t-butoxycarbonyl)-β-alanyl]-L-alanyl]amino]-ethyl]benzoate, m.p. 138-139°C.

f) After cleavage of the t-butoxycarbonyl group in trifluoroacetic acid, the product is reacted in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester.

Example 34

Analogously to Example 7, [DL-N-[N-(p-amidinobenzoyl)-β-alanyl-3-phenyl-β-alanine is obtained as the hydrate (3:1), m.p. 220°C (dec.), from DL-N-[N-[p-[N-[(benzyloxy)carbonyl]amidino]benzoyl]-β-alanyl]-3-phenyl-β-alanine benzyl ester.

The starting ester, m.p. 208°C, is obtained as follows:

a) N-(t-butoxycarbonyl)-β-alanine is reacted with

DL-3-phenyl-β-alanine benzyl ester to give DL-N-[N-(t-butoxycarbonyl)-β-alanyl]-3-phenyl-β-alanine benzyl ester, m.p. 124.5-126°C.

b) The trifluoroacetate of DL-N-(β-alanyl)-3-phenyl-β-alanine benzyl ester is obtained therefrom in trifluoroacetic acid.

c) This is reacted in methylene chloride/water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester.

Example 35

Analogously to Example 11, [p-[2-[[N-[N-(p-amidinobenzoyl)-β-alanyl]-L-α-aspartyl]-amino]ethyl]-phenoxy]acetic acid is obtained as the hydrate (2:7), m.p. 210-213°C, from benzyl (S)-3-[[N-[p-[N-[(benzyloxy)-carbonyl]amidino]benzoyl]-β-alanyl]amino]-N-[p-[[(benzyloxy)carbonyl]methoxy]phenethyl]succinamate.

The starting ester, m.p. 172-174°C, can be prepared as follows:

a) t-Butyl [2-(4-hydroxyphenyl)ethyl]carbamate, benzyl bromoacetate and potassium carbonate are heated in acetone. t-Butyl [p-[[(benzyloxy)carbonyl]-methoxy]-phenethyl]carbamate, MS: 385 (0.5, M), is obtained.

b) After cleavage of the t-butoxycarbonyl protecting group, the product is coupled with N-(t-butoxycarbonyl)-aspartic acid-4-benzyl ester to give benzyl (S)-N-[p-[[(benzyloxy)carbonyl]methoxy]phenethyl]-3-[1-t-butoxy-formamido]succinamate, m.p. 178.5-180.5°C.

c) This is deprotected in trifluoroacetic acid and coupled with N-(t-butoxycarbonyl)-β-alanine to give t-butyl [2-[[(S)-2-[(benzyloxy)carbonyl]-1-[[p-[[(benzyl-oxy)carbonyl]methoxy]-phenethyl]carbamoyl]ethyl]-carbamoyl]ethyl]carbamate, m.p. 123-124°C.

d) After cleavage of the t-butoxycarbonyl protecting group, the product is reacted in methylene chloride/-water/sodium bicarbonate with p-amidinobenzoyl chloride and subsequently with benzyl chloroformate to give the starting ester.

Example 36

a) A solution of 280 mg of 1-[N-(p-cyanobenzoyl)-β-alanyl]-4-piperidinoacetic acid and 1 ml of triethylamine in 15 ml of pyridine is saturated with hydrogen sulphide. After 36 hours, the solution is evaporated and the residue is suspended in ethyl acetate/water. Filtration and drying of the insoluble material gives 255 mg of 1-[N-[p-(thiocarbamoyl)benzoyl]-β-alanyl]-4-piperidinoacetic acid.

b) A solution of 150 mg of the precursor in 15 ml of acetone is heated to boiling temperature with 1 ml of methyl iodide for 2 hours. After cooling the solution to room temperature, 130 mg of 1-[N-[p-[1-(methylthio)formimidoyl]benzoyl]-β-alanyl]-4-piperidinoacetic acid hydroiodide (1:1), m.p. 206-207°C, precipitate.

c) 100 mg of 1-[N-[p-[1-(methylthio)formimidoyl]-benzoyl]-β-alanyl]-4-piperidinoacetic acid and 30 mg ammonium acetate in 10 ml of methanol are kept at boiling temperature for 3 hours. After cooling to room temperature, the solution is filtered, concentrated and treated with diethyl ether. The precipitated oil is chromatographed on silica gel RP 18 using water/methanol (10:1) after decanting of the solvent. 24 mg of 1-[N-(p-amidinobenzoyl)-β-alanyl]-4-piperidinoacetic acid hydroiodide (10:1), m.p. 206°C, are obtained.

The starting nitrile can be obtained as follows:

a) 4.96 g of 4-cyanobenzoyl chloride and 2.67 g of β-alanine are stirred at room temperature for 4 hours in 450 ml of sodium bicarbonate solution (2%) and the mixture is acidified using concentrated sulphuric acid (pH 6). The solution is evaporated and extracted using ethyl acetate. Drying and evaporation of the organic phase gives a residue which, with diisopropyl ether, leads to 4.69 g of N-(p-cyanobenzoyl)-β-alanine, m.p. 155-157°C.

b) Coupling of 635 mg of N-(p-cyanobenzoyl)-β-alanine with 540 mg of 4-piperidinoacetic acid gives, after chromatography on silica gel RP 18 using THF/water (85:15) 300 mg of 1-[N-(p-cyanobenzoyl)-β-alanyl]-4-piperidinoacetic acid, MS: 344 $(M-H)^-$.

Example 37

400 mg of t-butyl 4-[N-(p-amidinobenzoyl)-β-alanyl]-1-piperazinoacetate are stirred in 15 ml of methylene chloride and 15 ml of trifluoroacetic acid. The solution is evaporated, the residue is suspended in 5 ml of ethanol and the undissolved material is filtered off. The filtrate is treated with ethyl acetate and the precipitate is filtered with suction and dried. Chromatography of the crude product on silica gel RP 18 using water leads to 38 mg of 4-[N-(p-amidinobenzoyl)-β-alanyl]-1-piperazinoacetic acid trifluoroacetate (5:8), m.p. 157-.58°C.

The starting material can be prepared as follows:

a) 2.23 g of N-benzyloxycarbonyl-β-alanine are coupled with 2.58 g of piperazine. The evaporation residue is suspended in THF, the undissolved material is filtered off and the filtrate is evaporated. Chromatography of the residue on silica gel RP 18 using water/methanol (2-5%) gives 2.51 g of benzyl [2-(4-piperazinylcarbonyl)ethyl]-carbamate, MS: 291 (M^+).

b) 600 mg of the precursor, 0.3 ml of t-butyl bromoacetate and 2.5 mg of tetrabutylammonium hydrogen sulphate are dissolved in 10 ml of toluene and stirred with 10 ml of 50 % strength sodium hydroxide solution for 1 hour. The organic phase is washed with water and evaporated. Chromatography of the residue on silica gel using ethyl acetate/methanol (9:1) gives 480 mg of t-butyl 4-[N-[(benzyloxy)carbonyl]-β-alanyl]-1-piperazinoacetate, MS: 406 $(M-H)^+$.

c) The precursor is hydrogenated in ethanol for 1 hour in the presence of 200 mg of Pd/C. The catalyst is filtered off and the filtrate is evaporated. 290 mg of t-butyl 4-β-alanyl-1-piperazinoacetate, MS: 271 (M^+), are obtained.

d) The precursor and 341 mg of p-amidinobenzoyl chloride are stirred in 20 ml of methylene chloride and 10 ml of saturated sodium bicarbonate. The organic phase is separated off and evaporated, and the residue is suspended in ethyl acetate. Filtration with suction and

drying of the crystals gives 400 mg of t-butyl 4-[N-(p-amidinobenzoyl)-β-alanyl]-1-piperazinoacetate, MS: 419 $(M-H)^+$.

Example 38

Analogously to Example 37, 1.6 g of N-[N-[N-(p-amidinobenzoyl)-β-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-L-valine t-butyl ester are deprotected. The crude product is chromatographed on silica gel RP 18 using water/THF (95:5). 867 mg of N-[N-[N-(p-amidinobenzoyl)-β-alanyl]-L-α-aspartyl]-L-valine trifluoracetate, m.p. 162-163°C, are obtained.

The starting ester can be prepared as follows:

a) t-Butyl N-benzyloxycarbonyl-L-α-aspartate and L-valine t-butyl ester hydrochloride are coupled to give N-[N-[(benzyloxy)carbonyl]-3-(t-butoxycarbonyl)-L-alanyl]-L-valine t-butyl ester, m.p. 75°C (d).

b) This is deprotected analogously to Example 37c. N-[3-t-butoxycarbonyl)-L-alanyl]-L-valine t-butyl ester, m.p. 71°C, is obtained.

c) 2.8 g of the precursor are coupled with 1.78 g of N-[(benzyloxy)carbonyl]-β-alanine and the crude product is chromatographed on silica gel using ethyl acetate. 2.24 g of N-[N-[N-[(benzyloxy)carbonyl]-β-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-L-valine t-butyl ester, m.p. 126°C are obtained.

d) Deprotection of 2.2 g of the precursor analogously to Example 37c) leads to 1.61 g of N-[N-β-alanyl-3-(t-butoxycarbonyl)-L-alanyl]-L-valine t-butyl ester.

e) Reaction of 1 g of p-amidinobenzoyl chloride with 1.61 g of the precursor according to procedure 37d gives 1.62 g of starting ester.

Example 39

Analogously to Example 37, 1.4 g of N-[N-[N-(p-amidinobenzoyl)-β-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-(p-t-butoxyphenyl)-L-alanine t-butyl ester are deprotected. The product is suspended in ethanol, insoluble material is filtered off and the filtrate is treated with ether. Filtration with suction and washing of the precipitate with 20 ml of isopropanol/ethanol (1:1) gives

801 mg of N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-(α-aspartyl]-3-(p-hydroxyphenyl)-L-alanine trifluoroacetate (2:5), m.p. 202-204°C.

The starting ester can be prepared as follows:

a) N-[(9H-fluoren-9-yloxy)carbonyl]-3-(t-butoxycarbonyl)-L-alanine and 3-(p-t-butoxyphenyl)-L-alanine t-butyl ester are coupled to give N-[N-[(9H-fluoren-9-yloxy)carbenyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-(p-t-butoxyphenyl)-L-alanine t-butyl ester and 5 ml of piperidine and the reaction solution is evaporated. The residue is suspended in methanol and insoluble material is filtered off. The filtrate is evaporated and chromatographed on silica gel using ethyl acetate. 2 g of 3-(t-butoxyphenyl)-N-[3-(p-t-butoxy-carbonyl)-L-alanyl]-L-alanine t-butyl ester are obtained.

c) The precursor is coupled with 0.96 g of N-benzyloxycarbonyl-ß-alanine and the crude product is chromatographed on silica gel using ethyl acetate. 2.23 g of N-[N-[N-[(benzyloxy)carbonyl]-ß-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-(p-t-butoxyphenyl)-L-alanine t-butyl ester, MS: 670 $(M+H)^+$, are obtained.

d) Deprotection of 2.1 g of the precursor as in Example 37c) gives 1.67 g of N-[N-ß-alanyl]-3-(t-butoxycarbonyl)-L-alanyl]-3-(p-t-butoxyphenyl)-L-alanine t-butyl ester, MS: 536 $(M+H)^+$.

e) Coupling of 1.5 g of the precursor with 0.6 g of p-amidinobenzoyl chloride as in Example 37d) gives 1.6 g of starting ester, MS: 682 $(M+H)^+$.

Example 40

Analogously to Example 24 there is obtained N-[N-[N-[(5-amidino-2-pyridyl)carbonyl]-β-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine, m.p. 222-223°C (dec.) from the corresponding ester.

The starting ester can be prepared as follows:

a) N-[3-[(Benzyloxy)carbonyl]-N-[N-(t-butoxycarbonyl)-β-alanyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester is deprotected and coupled with 5-cyano-2-pyridinecarboxylic acid to give N-[3-[(benzyloxy)carbonyl]-N-[N-[(5-cyano-2-pyridyl)carbonyl]-β-alanyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester, m.p. 157-158°C.

b) The precursor is converted as in Example 36a) into N-[3-[(benzyloxy)-carbonyl]-N-[N-[[5-(thiocarbamoyl)-2-pyridyl]carbonyl]-β-alanyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester, m.p. 131-132°C.

c) The precursor is converted as in Example 36b) and c) into N-[3-[(benzyloxy)carbonyl]-N-[N-[[5-[N-(t-butoxycarbonyl)amidino]-2-pyridyl]-carbonyl]-β-alanyl]-L-alanyl]-3-phenyl-L-alanine benzyl ester, MS: 779 (11,M+H).

Example A

A compound of the formula I can be used in a manner known per se as an active compound for the production of tablets of the following composition:

	per tablet
Active compound	200 mg
microcrystalline cellulose	155 mg
cornflour	25 mg
talc	25 mg
hydroxypropylmethylcellulose	20 mg
	425 mg

Example B

A compound of the formula I can be used in a manner known per se as an active compound for the production of capsules of the following composition:

	per capsule
Active compound	100.0 mg
cornflour	20.0 mg
lactose	95.0 mg
talc	5 mg
magnesium stearate	0.5 mg
	220.0 mg

Patent Claims

1. Acetic acid derivative of the formula

$H_2N(NH)C\text{-}X\text{-}Y\text{-}CO\text{-}Z\text{-}CH(Q^1)COOQ^2$ (I)

in which

Q^1 is hydrogen, methyl or phenyl,

Q^2 is hydrogen, phenyl-lower alkyl or lower alkyl which can be cleaved under physiological conditions,

X is 1,4-phenylene, 1,4-piperidinylene bound via the C atom in the 4-position to the group Y, or 2,5- or 3,6-pyridylene

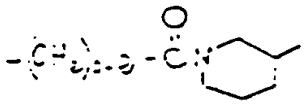
Y is a group of the formula

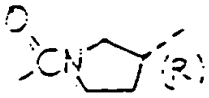
$-(CH_2)_{0-2}\text{-}CONHCH(Q^3)(CH_2)_{1-3}$- ($Y^1$)

$-CONHCH_2CH(Q^4)$- (Y^2)

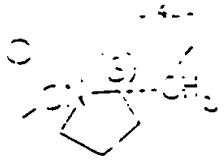
$-(CH_2)_2NHCOCH_2$- (Y^3)

$-NHCO(CH_2)_3$- (Y^4)

 (Y^5)

 (Y^6)

or



(Y7)

Q^3 is hydrogen, methyl, phenyl, -COOH, -COO-lower alkyl, -CONH$(CH_2)_2$-COOH or -CONH$(CH_2)_2$-COO-lower alkyl,

Q^4 is hydrogen, methyl or phenyl,

Z is a 1,4-piperazinylene group, a 1,4-piperidinylene group bound via the N-atom in the 1-position to the CO group, or a group of the formula

-NHCH(R^1)- or -NHCH(COR^2)-

R^1 is hydrogen, methyl, phenyl or -COO-lower alkyl,

R^2 is the radical of an α-aminocarboxylic acid bound via the amino group or an ester or amide thereof, or a group of the formula -NHCH$_2$CH$_2$-Ar, or

-CO-R^2 is an optionally mono- or di-lower-alkylated carbamoyl group or a pyrrolidinoyl or piperidinoyl group,

Ar is phenyl or phenyl which is substituted by lower alkyl, lower alkoxy, -COOH, -COO-lower alkyl, -O$(CH_2)_{1-4}$-COOH, -O$(CH_2)_{1-4}$-COO-lower alkyl, -CONH$_2$, -CONH-lower alkyl, -CON(lower alkyl)$_2$, pyrrolidinoyl or piperidinoyl,

and hydrates or solvates and physiologically utilisable salts thereof.

2. Compounds according to Claim 1 and of the formula

$H_2N(HN)C$-X-Y^a-CONHCH(R^{11})CH_2COOQ^{21} I-A

in which

X is 1,4-phenylene or 1,4-piperidinylene bound via the C atom in the 4-position to the group Y^a,

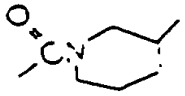
Y^a is a group of the formula

-$(CH_2)_{0-1}$-CONHCH(Q^a)$(CH_2)_{1-2}$- (Y11)

-$(CH_2)_2$NHCOCH_2- (Y3)

-NHCO$(CH_2)_3$- (Y4)

or



(Y51)

Q^a is hydrogen or phenyl,

R^{11} is hydrogen or -CO-R^{22},

R^{22} is the radical of an α-aminocarboxylic acid bound via the amino group or of an ester or amide thereof, and

Q^{21} is hydrogen or lower alkyl which can be cleaved under physiological conditions,

and hydrates or solvates and physiologically utilisable salts thereof.

3. Compounds according to Claim 1, in which X, Z, Q^1 and Q^2 have the meaning indicated in Claim 1 and Y is a group of the formula Y^1, in particular one of the formula

-CONH$(CH_2)_{2-4}$-,
-CH_2CONH$(CH_2)_2$-,
-CONHCH$(C_6H_5)CH_2$-,
-CONHCH(CONHCH$_2$CH$_2$COOH)CH$_2$-,
-CONHCH(COOH)CH$_2$- or
-CONHCH$(CH_3)CH_2$-.

4. Compounds according to Claim 1, in which X, Y, Q^1 and Q^2 have the meaning indicated in Claim 1 and Z is a group of the formula -NHCH$_2$-, -NHCH(CH_3)-, -NHCH(C_6H_5)-, -NHCH(COO-isobutyl)-, -NHCH(CO-Val)-, -NHCH(CO-Phe)-, -NHCH(CO-Tyr)-, -NHCH(CO-Ser-OC_2H_5)-, -NHCH(CO-Leu-O-iso-propyl)-, -NHCH(CONHCH$_2$CH$_2$-C_6H_4-OCH$_3$)-, -NHCH(CONHCH$_2$CH$_2$-C_6H_4-COOH)-, -NHCH(CONHCH$_2$CH$_2$-C_6H_4-OCH$_2$COOH)-, -NHCH(CONH$_2$)- or -NHCH(pyrrolidinoyl)-.

5. Compounds according to Claim 2 from the group comprising the following:

N-[N-[4-(p-amidinobenzamido)butyryl]-L-α-aspartyl]-L-valine,
N-[N-(p-amidinobenzoyl)-ß-alanyl]-ß-alanine and in particular
N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine.

6. Compounds according to Claim 2 from the group comprising the following:

N-[N-[N-(1-amidino-4-piperidinylcarbonyl)-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine,
N-[N-[N-(p-amidinophenylacetyl)-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine,
N-[N-[4-(p-amidinophenylcarbamoyl)butyryl]-L-α-aspartyl]-3-phenyl-L-alanine,
N-[N-[(p-amidinophenylcarbamoyl)acetyl]-L-α-aspartyl]-3-phenyl-L-alanine,

rac-N-[1-(p-amidinobenzoyl)-3-piperidinylcarbonyl]-ß-alanine,
N-[4-(p-amidinobenzamido)butyryl]-ß-alanine and
N-[(DL)-N-(p-amidinobenzoyl)-3-phenyl-ß-alanyl]-ß-alanine.

7. Compounds according to Claim 1 from the group comprising the following:

N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-L-leucine isopropyl ester,
N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-L-valine,
N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-3-(p-hydroxyphenyl)-L-alanine,
N-[N-[5-(p-amidinobenzamido)valeryl]-L-α-aspartyl]-3-phenyl-L-alanine,
isobutyl N-[5-(p-amidinobenzamido)valeryl]-L-α- aspartate,
N-[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-L-serine ethyl ester and
N-[N-[[(R)-1-(p-amidinobenzoyl)-3-pyrrolidinyl]carbonyl]-L-α-aspartyl]-3-phenyl-L-alanine.

8. Compounds according to Claim 1 from the group comprising the following:

N,N'-[[(S)-(p-amidinobenzamido)ethylene]dicarbonyl]di-ß-alanine,
2-N-(p-amidinobenzoyl)-4-N-(2-carboxyethyl)-L-asparagine,
N-[5-(p-amidinobenzamido)valeryl]-ß-alanine,
rac-N-[[1-[3-(1-amidino-4-piperidinyl)propionyl]-3-piperidinyl]carbonyl]-ß-alanine,
N-[[(S)-1-(p-amidinobenzoyl)-2-pyrrolidinyl]acetyl]-ß-alanine,
(S)-3-[[N-(p-amidinobenzoyl)-ß-alanyl]amino-3-[(p-methoxyphenethyl)-carbamoyl]propionic acid,
N-[[(R)-1-(p-amidinobenzoyl)-3-pyrrolidinyl]carbonyl]-ß-alanine,
N-[N-(p-amidinobenzoyl)-2-methyl-ß-alanyl]-L-α-aspartamide,
N-[N-[(p-amidinophenyl)acetyl]-ß-alanyl]-ß-alanine,
rac-N-[[[1-(p-amidinophenyl)acetyl]-3-piperidinyl]-carbonyl]-ß-alanine benzyl ester,
rac-N-[[1-[(p-amidinophenyl)acetyl]-3-piperidinyl]-carbonyl]-ß-alanine,
N-[N-[N-[3-(1-amidino-4-piperidinyl)propionyl]-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine,

(S)-ß-[[DL-N-(p-amidinobenzoyl)-3-methyl-ß-alanyl]amino]-γ-oxo-1-pyrrolidinebutyric acid,

DL-N-[N-(p-amidinobenzoyl)-ß-alanyl]-3-methyl-ß-alanine,

N-[DL-N-(p-amidinobenzoyl)-2-phenyl-ß-alanyl]-ß-alanine,

DL-N-[N-(p-amidinobenzoyl)-ß-alanyl]-2-methyl-ß-alanine,

DL-N-[N-(p-amidinobenzoyl)-ß-alanyl]-2-phenyl-ß-alanine,

p-[2-[[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]-amino]ethyl]-benzoic acid,

DL-N-[N-(p-amidinobenzoyl)-ß-alanyl-3-phenyl-ß-alanine,

[p-[2-[[N-[N-(p-amidinobenzoyl)-ß-alanyl]-L-α-aspartyl]amino]-ethyl]phenoxy]acetic acid,

1-[N-(p-amidinobenzoyl)-ß-alanyl]-4-piperidineacetic acid,

4-[N-(p-amidinobenzoyl)-ß-alanyl]-1-piperazineacetic acid and

N-[N-[N-[(5-amidino-2-pyridyl)carbonyl]-ß-alanyl]-L-α-aspartyl]-3-phenyl-L-alanine.

9. Acetic acid derivates of the formula

$$X'\text{-}Y\text{-}CO\text{-}Z'\text{-}CH(Q^1)\text{-}COO\text{-}Q^2 \qquad II'$$

in which X' is phenyl or 4-piperidinyl substituted in the 4-position by an optionally protected amidino group, and Y, Z, Q^1 and Q^2 have the same meaning as in Claim 1, the molecule containing at least one easily cleavable ester group or protected amidino group.

10. Compounds according to one of Claims 1-8 for use as pharmaceutical active compounds.

11. Process for preparation of the compounds according to Claim 1, characterised in that

a) at least one protecting group is removed from a compound of the formula

$$X'\text{-}Y\text{-}CO\text{-}Z'\text{-}CH(Q^1)\text{-}COO\text{-}Q^5 \qquad II$$

in which

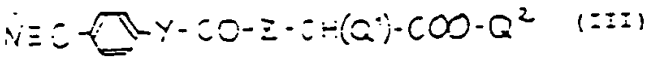
Q^1 and Y have the meaning indicated in Claim 1,

X' is phenyl or 4-piperidinyl which is substituted in the 4-position by an optionally protected amidino group, and

Z' and Q^5 have the same meaning as Z and Q^2 in Claim 1,

or

b) the nitrile group is converted into the amidino group in a nitrile of the formula



and, if desired, a compound of the formula I is converted into a physiologically tolerable salt, or a salt of a compound of the formula I into the free acid or base.

12. Pharmaceutical preparations, in particular for the treatment or prophylaxis of diseases which are caused by the binding of adhesive proteins to blood platelets, and also by blood platelet aggregation and cell-cell adhesion, containing a compound according to Claim 1 or 2 as the active compound.

13. Use of a compound according to Claim 1 or 2 for the production of medicaments for the treatment or prophylaxis of diseases which are caused by the binding of adhesive proteins to blood platelets, and also by blood platelet aggregation and cell-cell adhesion, in particular for the treatment or prophylaxis of blood platelet thrombi, thrombosis, cerebral infarct, myocardial infarct, inflammation or arteriosclerosis, or as anti-tumour agents or as agents for the healing of wounds.

14. The compounds of any one of claims 1-8, whenever prepared by the process of claim 11 or by an obvious chemical equivalent thereof.

15. The compounds, preparations, processes and uses as hereinbefore described, in particular with reference to the Examples.

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